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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,299	10/22/2003	Napoleone Ferrara	11669.0139USC1	9503

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,299	FERRARA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *13-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/04; 11/8/04; 6/10/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 1-25 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-12 drawn to polypeptide, filed 9/6/05, is acknowledged. The traversal is on the grounds that it would not be unduly burdensome to search Groups 1 and 2 together. This is not found persuasive because of the reasons set forth in the restriction mailed 8/12/05. With respect to the argument that the search and examination of all groups would not entail a "serious burden", the separate classification of the different groups provides prima facie evidence of such a burden; see MPEP § 803. Furthermore, polypeptides and polynucleotide represent different inventions and require different, non-contiguous searches, as evidenced by their different classification. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement is still deemed proper and is therefore made FINAL.

3. Claims 13-25 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1-12, drawn to polypeptide, are being acted upon in this Office Action.

5. The drawings, filed 10/22/03, are not approved. Specifically, Figures 8 and 9 are too dark. Appropriate action is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human endocrine gland-derived vascular endothelial growth factor (EG-VEGF) for screening assays, **does not** reasonably provide enablement for (1) any isolated polypeptide comprising any amino acid sequence having at least about 80%, 85%, 90%,

or 95% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein X is amino acid residue from 14 to 24 of SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) any isolated polypeptide "comprising" any amino acid sequence "comprises" amino acid residues X to 105 of SEQ ID NO: 2, wherein X is amino acid residue from 14 to 24 of SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (3) any isolated polypeptide "comprising" the amino acid sequence "comprises" amino acid residues 20 to 105 of SEQ ID NO: 2, (4) any isolated polypeptide "comprising" the amino acid sequence "comprises" the amino acid sequence "comprises" any amino acid sequence having at least 80% identity to SEQ ID NO: 2, (5) any isolated polypeptide comprising any amino acid sequence having at least about 80% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the amino acid sequence comprises SEQ ID NO: 2, (6) any isolated polypeptide comprising any amino acid sequence having at least about 80% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence of endocrine gland-derived vascular endothelial growth factor (EG-VEGF), (7) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is any allelic variant of EG-VEGF, (8) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is SEQ ID NO: 2, and (9) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is human EG-VEGF for treating any diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human EG-VEGF for screening agonist or antagonist (page 54-56) and production of antibody that binds specifically to EG-VEGF (See page 65). The specification further discloses that EG-VEGF is expressed in the endocrine tissues such as the stroma cell and granulose cells in the ovary, the Leydig cell in the testis, the adrenal gland and the placenta. The EG-VEGF is mitogenic and chemo attractant for specific endothelial cells but not human aortic vascular smooth muscle cells, pericytes, fibroblast, human neonatal fibroblasts and karatinocytes. The angiogenic effect of EG-VEGF is tissue specific since EG-VEGF has no effect on rat corneal pocket assay. The specification further discloses that injection of Adenoviral vector carrying the human EG-VEGF cDNA or VEGF causes an increase in angiogenesis, large fluid-filled or hemorrhagic cystic formation in ovary (Fig. 19).

The specification does not teach how to make and use *any* polypeptide mentioned above for treating any disease. This is because there is insufficient guidance as to which amino acids within the polypeptide from 14 to 105, 15 to 105, 16 to 105, 17 to 105, 18 to 105, 19 to 105, 20 to 105, 21 to 105, 22 to 105, 23 to 105 or 24 to 105 amino acids of SEQ ID NO: 2 to be substituted, deleted, added and/or combination thereof such that the resulting polypeptide having merely 80%, 85%, 90%, 95% sequence identity to X to 105 of SEQ ID NO: 2 wherein X is any amino acid residue from 14 to 24 of SEQ ID NO: 2 would maintain its structure and function. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because of the lack of disclosure about any polypeptide having any amino acid sequence that is 80%, 85%, 90%, 95% sequence identity to X to 105 of SEQ ID NO: 2 or any amino acid sequence that is 80% identity to SEQ ID NO: 2 and any "allelic variants" of SEQ ID NO: 2, it is unpredictable which undisclosed polypeptide has which function, in turn, would be useful for treating which disease. Further, the term "comprising", "comprises" or 'having" is open-ended. It expands the fragment from amino acid residues x to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added, hence the length of the polypeptide, and whether the resulting polypeptide still promotes proliferation of adrenal cortex-derived endothelial cells. Assuming the

undisclosed polypeptide still binds to its receptor and promotes proliferation, what disease could be treated without having the concern of cancer formation given the polypeptide has angiogenic property in the absence of in vivo working example.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495; PTO 1449). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al*, PTO 1449, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular).

Attwood *et al*, PTO 1449, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

Skolnick *et al*, PTO 1449, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Further, there is a lack of in vivo working example demonstrating the claimed polypeptide could treat *any* disease for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the *blood testicular barrier* or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Fogarty *et al*, PTO 1449, teach targeting angiogenesis using VEGF antagonist is a promising anticancer approach, however, the twelve recent failures in clinical trials using VEGF

antagonist, indicate the unpredictability of angiogenesis inhibitors for cancer treatment. Although the specification suggests that EG-VEGF, like VEGF, may be a potential cause of polycystic ovary syndrome (See Fig 19, in particular), no showing of the cause and effect has been demonstrated.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated polypeptide comprising any amino acid sequence having at least about 80%, 85%, 90%, or 95% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein X is amino acid residue from 14 to 24 of SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (2) any isolated polypeptide "comprising" any amino acid sequence "comprises" amino acid residues X to 105 of SEQ ID NO: 2, wherein X is amino acid residue from 14 to 24 of SEQ ID NO: 2 and wherein the polypeptide promotes proliferation of adrenal cortex-derived capillary endothelial cells, (3) any isolated polypeptide "comprising" the amino acid sequence "comprises" amino acid residues 20 to 105 of SEQ ID NO: 2, (4) any isolated polypeptide "comprising" the amino acid sequence "comprises" the amino acid sequence "comprises" any amino acid sequence having at least 80% identity to SEQ ID NO: 2, (5) any isolated polypeptide comprising any amino acid sequence having at least about 80% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the amino acid sequence comprises SEQ ID NO: 2, (6) any isolated polypeptide comprising any amino acid sequence having at least about

80% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the polypeptide is a native sequence of endocrine gland-derived vascular endothelial growth factor (EG-VEGF), (7) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is any allelic variant of EG-VEGF, (8) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is SEQ ID NO: 2, and (9) any isolated polypeptide comprising any amino acid sequence having at least about 80 identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein the native sequence is human EG-VEGF for treating any diseases.

The specification discloses only an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 2 wherein the polypeptide is a human EG-VEGF for screening agonist or antagonist (page 54-56) and production of antibody that binds specifically to EG-VEGF (See page 65). The specification further discloses that EG-VEGF is expressed in the endocrine tissues such as the stroma cell and granulose cells in the ovary, the Leydig cell in the testis, the adrenal gland and the placenta. The EG-VEGF is mitogenic and chemo attractant for specific endothelial cells but not human aortic vascular smooth muscle cells, pericytes, fibroblast, human neonatal fibroblasts and karatinocytes. The angiogenic effect of EG-VEGF is tissue specific since EG-VEGF has no effect on rat corneal pocket assay. The specification further discloses that injection of Adenoviral vector carrying the human EG-VEGF cDNA or VEGF causes an increase in angiogenesis, large fluid-filled or hemorrhagic cystic formation in ovary (Fig. 19).

With the exception of the specific polypeptide comprising SEQ ID NO: 2, there is insufficient written description about the structure associated with function of any and all polypeptide comprising any amino acid sequence having at least about 80%, 85%, 90%, or 95% identity to amino acid residues X to 105 of SEQ ID NO: 2, wherein X is amino acid residue from 14 to 24 of SEQ ID NO: 2 without the amino acid sequence. Further, the disclosure fails to adequately describe which amino acids within the SEQ ID NO: 2 to be substituted, deleted, added and/or combination thereof. The term "comprising", "comprises" or 'having" is open-ended. It expands the fragment from amino acid residues x to 105 of SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of disclosure about which amino acids to be added, hence the length of the polypeptide is not adequately described. Finally, the disclosure does not adequate describe the structure of the "allelic variant" of any EG-VEGF without the amino acid sequence.

The specification discloses only human EG-VEGF comprising SEQ ID NO: 2, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of allelic variants to describe the genus for the claimed polypeptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. SEQ ID NO: 2 is free of prior art.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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